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Invited Editorial Comment

Vasopressin-2 Receptor Antagonists in Autosomal Dominant Polycystic Kidney Disease: From Man to Mouse and Back

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Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent inherited nephropathy, with an estimated prevalence of 1 to 1000. The disease is characterized by the development of multiple cysts from all nephron segments leading to the enlargement of both kidneys and replacement of normal parenchyma (1, for review). Total kidney volume is the strongest predictor of renal function decline in ADPKD (2). Glomerular filtration rate (GFR) remains preserved up to age 40 in most patients, because glomerular hyperfiltration in functioning nephrons compensates for the ongoing loss of renal tissue, until end-stage renal failure ensues in more than 50% of patients, usually in their 5th decade. Mutations in the *PKD1* gene account for ~85% of the affected families, whereas the remaining cases are caused by mutations in *PKD2*. *PKD1* encodes polycystin-1, an integral membrane protein with a large extracellular domain that probably functions as a receptor and/or an adhesion molecule, whereas *PKD2* encodes polycystin-2, a non-selective cation channel belonging to the family of transient receptor potential (TRP) channels. The polycystins interact to form a mechanosensory complex that is involved in intracellular Ca^{2+} homeostasis and various signalling pathways. Disruption of the complex leads to cyst development and enlargement resulting from tubular cell proliferation and transepithelial fluid secretion. The progressive understanding of these pathways has led to spectacular advances in the prospective treatment for ADPKD, including the blockade of vasopressin 2 receptor (V2R) to decrease the intracellular level of 3'-5'-cyclic adenosine monophosphate (cAMP) in cyst-lining tubular cells (1).

Vasopressin and cAMP in ADPKD

The vasopressin V2 receptor is the major regulator of adenylyl cyclase activity and of cAMP production in the principal cells of the collecting ducts. Increased levels of cAMP and high expression of cAMP-target genes have been observed in the cystic kidneys of various rodent

models, which could arise from decreased intracellular Ca^{2+} concentration caused by mutations in polycystins 1/2, via the downregulation of phosphodiesterase PDE and stimulation of the Ca^{2+}-inhibitable adenylyl cyclase 6 (1). In turn, the increased production of cAMP stimulates the proliferation and growth of ADPKD cells and drives Cl^- and fluid secretion via PKA-stimulated CFTR and, potentially, other transport processes located in the apical and basolateral membranes (3).

The importance of the V2R-cAMP pathway has been demonstrated by the spectacular effects of the V2R antagonists (V2RA) OPC-31260 and Tolvaptan on lowering renal cAMP levels, slowing renal cyst growth and improving renal function in various models of autosomal recessive (PCK rat) and autosomal dominant (*Pkd2*$^{WS25/-}$ mouse) polycystic kidney disease (4). Similar protection has been observed when vasopressin secretion is inhibited by high water intake in PCK rats (5). Furthermore, the deletion of vasopressin in these PCK rats (by crossing them to Brattleboro rats) led to lower renal cAMP levels and an almost complete inhibition of cystogenesis, whereas administration of dDAVP recovered the cystic phenotype in the PCK x Brattleboro rats (6). Based on these preclinical studies, a phase III clinical trial investigating the effect of the highly-selective V2R antagonist Tolvaptan (OPC-41061) in ADPKD patients (TEMPO ¾) has been initiated in 2007 (7). This trial enrolled more than 1,400 ADPKD patients with relatively preserved kidney function (baseline estimated creatinine clearance ≥60 mL/min), aged 50 years or younger, and with total kidney volume ≥750 mL (MRI measurement). Blockade of vasopressin V2 receptor is hypothesized to inhibit cyst growth, thereby delaying ADPKD-associated complications including kidney function decrease, blood pressure control, and flank pain.

V2R antagonists in *Pkd1* mice

The aim of the TEMPO ¾ trial is to examine whether Tolvaptan at high dose is able to slow renal cystic progression in a preselected ADPKD population at a relatively early stage of disease and with a risk of progression to kidney failure. Independent of the final study outcome, this trial will leave important questions open, in particular the potential interest of V2RA for patients with more advanced disease and their efficacy at lower doses which should decrease the side-effects (polyuria and nycturia) and thus improve tolerance. The investigations performed in a *Pkd1* mouse model by Meijer et al. (P XX of this issue) provide interesting insights in these issues (8). The study is based on the oral administration of OPC-31260 at high (0.1%) or low (0.05%) dose, 10 days after the specific deletion of *Pkd1* in renal tubular epithelium in 11-day old mice (using a tamoxifen-inducible Cre system). After a 3-week or 6-week treatment (late vs. early intervention, respectively), the mice were sacrificed and sampled to monitor renal function parameters and kidney cyst growth.

The first finding is that an early (starting at 3 weeks of age) and short-term (3 weeks) treatment of this *Pkd1* mouse model with high dose of V2RA resulted in a significant aquaretic effect and attenuation of the renal cystic phenotype (estimated by relative cyst area and kidney weight) as compared with untreated *Pkd1*-deleted mice. These results confirm some of the V2RA effects observed in other polycystic mouse models (4), although the treatment did not ameliorate renal function and was not shown to lower cAMP levels and decrease the expression of target genes in this model (8). Secondly, the protective effect on the renal cystic phenotype is no longer observed after long-term (6 weeks) administration of the V2RA, even at high dose. This treatment escape is paralleled by a lower aquaretic response to the V2RA, as attested by less marked changes in the urinary volume, urinary osmolality and water intake parameters at week 6 vs. week 3. It must be noted that the intake of V2RA remained similar between the two time

points, whereas the mRNA expression of V2R was significantly decreased at week 6. The third finding of the study is the fact that administration of V2RA at a more advanced stage of disease (6 weeks of age, late intervention) induced a lower aquaretic response and showed no effect on cyst growth. Based on these findings, the authors conclude that intervention with V2RA should be initiated early in the course of the disease, at high dose, and that combination therapy may be needed to reduce cystogenesis at a later stage.

From the *Pkd1* mice to ADPKD patients

The results of Meijer et al. (8) raise several points regarding the translation of animal study results to human ADPKD. The discordance between encouraging preclinical studies and disappointing results of two clinical trials using mTOR inhibitors (9,10) has pointed to issues such as drug dosage, time of treatment initiation, duration of administration, choice of end-point and surrogate markers and, most importantly, relevance of the preclinical models used to test drugs and predict human outcomes (11). The mouse model used by Meijer et al. arises from the deletion of the *Pkd1* gene (orthologous to human *PKD1*) in mouse. However, the kidney-specific loss of *Pkd1* occurs at once, in the early post-natal phase, and it is segment-specific, reflecting the expression of Cre recombinase (8). These characteristics are very different from the two-hit model, which remains the most commonly accepted explanation for the focal and clonal nature of cystogenesis in human ADPKD (1). Elegant studies have also demonstrated that the very timing of *Pkd1* inactivation plays a major role in the cystogenesis profile in mouse models (12). These factors probably explain the significant phenotype variations observed in different models. For instance, the *Pkd1* mice used by Meijer et al. show a majority of cysts stained for uromodulin, a specific marker of the thick ascending limb of Henle's loop (13), whereas only 20% of cysts, generally smaller, are positive for aquaporin-2 (AQP2), and no cysts positive for proximal tubule

markers (8). This profile is clearly distinct from what is observed in other models of *Pkd1* or *Pkd2* inactivation (14,15). In human ADPKD, Bachinski et al. located AQP1 in a majority (~70%) of cysts of proximal tubule origin (gp330 positive), whereas a minority of the cysts, negative for AQP1 and gp330, expressed AQP2 (16). Devuyst et al. confirmed the selective and mutually exclusive expression of AQP1 and AQP2 in various stages of ADPKD (17). In end-stage ADPKD, two-thirds of the cysts expressed either AQP1 or AQP2, but the two water channels never colocalized in the same cyst. Of note, the proportion of AQP2-positive cysts significantly increased with cyst size, supporting a role for vasopressin in cyst enlargement (17).

An intriguing observation made by Meijer et al. is the decreased efficacy of the high-dose V2RA over time, with no significant protection observed after 6-week treatment. The authors show that this is not due to a lower intake of the drug (as estimated by food intake), nor to increased endogenous vasopressin levels (as estimated from unchanged copeptin precursor), and the global mRNA expression of the V2R was actually lower at this stage (8). Differences in pharmacokinetics and timing and/or insufficient inhibition of the V2R in this model constitute a potential explanation. Indeed, significant effects on renal cystogenesis and function were observed in the *Pkd2* mouse model after 12 weeks of treatment with 0.05% OPC31260 (15). Alternatively, changes in down-stream effectors of vasopressin action in the collecting duct cells, which can be affected by polycystin-1 dosage, could also play a role (18). Finally, these findings may suggest that the timing of *Pkd1* inactivation in this model triggers cystogenesis via temporally and spatially distinct pathways in different tubular segments, so that the effect of V2R blockage on cysts arising from the collecting ducts may only be partial and limited in time. If proved true, this mechanism of cystogenesis would necessitate to combine various drugs targeting these segment-specific pathways of cystogenesis.

Two final considerations should be made when extrapolating these mouse studies to man. First, the timing of intervention (treatment started at 3 weeks of age in the early intervention group) is in fact very early when considering that significant changes in renal tubular maturation occur up to 6 to 8 weeks of age in mouse (19,20). In man, such an early intervention would mean to treat young children, with potential long-term consequences due, among others, to prolonged polyuria (21). Second, there are species differences in the functional effect of vasopressin in the distal nephron (thick ascending limbs and collecting ducts), which probably sustain the much higher urinary concentrating capacity of the rodents as compared to man (22). Furthermore, the segmental distribution of the V2 receptors in mouse and human kidney remains debated (23,24). The effect of V2R blockade in any rodent model should thus be interpreted carefully in view of these potential differences.

Conclusions

Since cyst expansion is a major factor for the progressive deterioration and loss of renal function in ADPKD, therapies targeting fluid secretion and, thereby, cyst enlargement are of major clinical interest. The study of Meijer et al. provides further support for the effect of V2RA on slowing cyst growth in ADPKD, shown for the first time in a *PKD1* orthologous model (8). Although this effect is not reflected by protection in terms of renal function and fibrosis in this model, these findings suggest that the V2RA treatment should be initiated very early in the disease, and with high dose inducing a strong aquaretic effect. The fact that V2RA effect is not sustained supports the view that cystogenesis may be a dynamic process involving different segments during the disease course. Moreover, these results emphasize the need for better characterization of disease mechanisms and species differences when considering the preclinical models used to investigate new therapeutic targets.

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DISCLOSURE

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